Final Registration of Isoxaflutole on Isoxaflutole–Resistant Soybeans

United States Environmental Protection Agency

Office of Pesticide Programs

Registration Division

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I. Summary

This document announces that the U.S. Environmental Protection Agency (EPA or the agency) has granted an unconditional, 5-year registration under section 3(c)(5) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) for the new use of the herbicide isoxaflutole on genetically modified, isoxaflutole-resistant soybeans. The new use will be initially added to the currently registered product Balance Pro Herbicide (EPA Registration Number 264-600), which contains 40.5% of the active ingredient isoxaflutole, for pre-plant, pre-emergence, or post-emergence (over-the-top) application to isoxaflutole-resistant soybeans. Immediately following the registration of isoxaflutole on isoxaflutole resistant soybeans, the registration will be transferred from Bayer Crop Sciences to BASF who will then launch the new soybean use under the brand name Alite™ 27 herbicide (EPA reg # 7969-433). Concurrently with this transfer, Bayer Crop Science will no longer maintain a soybean use on Bayer's above-mentioned end-use product.

The new use for isoxaflutole has been granted a registration in specific counties in the following states: Arkansas, Colorado, Georgia, Indiana, Kansas, Kentucky, Louisiana, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, New Mexico, North Carolina, North Dakota, Ohio, Oklahoma, Pennsylvania, South Dakota, Tennesse, Texas, Virginia, West Virginia, and Wisconsin.

Tolerances (i.e., maximum allowable pesticide residue levels) for isoxaflutole in/on soybeans that support this action have been established under title 40 of the United States Code of Federal Regulations (40 CFR) Section 180.537 under 408(d) of the Federal Food, Drug and Cosmetics Act (FFDCA) and are adequate to support the new registered use.

This final decision document summarizes EPA's risk assessments and its findings. For detailed information, refer to the documents listed in the references section which are accessible in the public docket at *www.regulations.gov* under docket number EPA-HQ-OPP-2019-0398.

II. Background

On July 6, 2010, EPA received an application from Bayer CropScience LP (Bayer) to register a new use of isoxaflutole as a pre-plant, pre-emergence, or post-emergent (over-the-top) application to isoxaflutole-resistant soybeans.

On December 7, 2011 a final rule was published in the Federal Register to establish tolerances for residues on isoxaflutole in/on soybean commodities.

The new registered use of the herbicide isoxaflutole must be paired in the field with special soybean seed which have been engineered to be resistant to this chemical. Under the regulatory oversight conducted at the federal level for biotechnology, the U.S. Department of Agriculture (USDA) is responsible for evaluating and approving genetically engineered seed. In this case,

the USDA granted deregulated status for isoxaflutole resistant soybean seed on August 21, 2013 under the Plant Protection Act.

Use Profile

Isoxaflutole is a 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitor (Weed Science Society of America (WSSA) Group 27) herbicide registered for control of broadleaf and grass weeds in corn, which is naturally resistant to isoxaflutole formulations containing a safener additive. Its primary target site of action in plants is inhibition of the enzyme HPPD, resulting in plant bleaching due to the blockage of phenylquinone biosynthesis in the plant tissue. Isoxaflutole is a selective herbicide now registered for control of broadleaf and grass weeds infesting soybeans when used as a preplant, preemergence, or early postemergence herbicide. The registered product, Balance Pro Herbicide (EPA Reg. No. 264-600), is formulated as a 40.5% soluble concentrate of isoxaflutole at a concentration of 4.0 pounds per gallon. Isoxaflutole is the sole active ingredient in Balance Pro Herbicide and the related BASF product , Alite™ 27 herbicide, which will initially be the sole product available for use on soybeans that have been genetically engineered to be resistant to isoxaflutole.

The current and forthcoming registered products are Restricted Use Pesticides (RUPs). Also, the approved applications are made as a foliar spray by ground equipment only.

III. Regulatory Determination Process

For this action, EPA assessed dietary and non-dietary human health risks, environmental risks including risks to non-target plants and wildlife, including endangered species, weed-resistance risk, and economic and biological benefits of isoxaflutole use on isoxaflutole-resistant soybeans. FIFRA requires pesticides distributed or sold in the United States to be registered by EPA based on scientific data showing that they will not cause "unreasonable adverse effects on the environment" when used in accordance with its product labeling.

For more information on how EPA regulates pesticides and conducts risk/benefit assessments, go to https://www.epa.gov/pesticide-registration/about-pesticide-registration and https://www.epa.gov/pesticide-registration/understanding-science-behind-epas-pesticide-decisions.

Evaluation of Risk to Human Health and the Environment

In evaluating a pesticide registration application, the EPA assesses a wide variety of exposure information (i.e., where and how the pesticide is used), environmental fate studies (i.e., how the chemical will move in the environment) and toxicity studies (i.e., effects on humans and other non-target organisms) to determine the likelihood of adverse effects (i.e., risk) from exposures associated with the registered use of the product. Risk assessments are developed to evaluate the environmental fate of the compound as well as how it might affect a wide range of non-target organisms including humans, terrestrial and aquatic wildlife and plants. On the basis of these

assessments, EPA evaluates and, as appropriate, approves language for each pesticide label to ensure the directions for use and safety measures are appropriate to mitigate potential risk so that it is not unreasonable. The pesticide's label helps to communicate essential limitations and mitigations that are necessary to ensure there are no unreasonable adverse effects. It is a violation of federal law to use a pesticide in a way that conflicts with the label.

A. Human Health Risk Assessment

EPA has evaluated the available toxicity data and considered its validity, completeness, and reliability as well as the relationship of the results of the studies to human risk. EPA has also considered available information concerning the variability of the sensitivities of major identifiable subgroups of consumers, including infants and children. The toxicology database for isoxaflutole is complete and adequate for hazard characterization.

All details regarding the human risk assessment are in the document entitled *Isoxaflutole. Section 3 Registration for Use on Soybeans. Human-Health Risk Assessment* which can be found at regulations.gov in docket ID number EPA-HQ-OPP-2010-0845.

Toxicological Profile

Isoxaflutole demonstrated low acute toxicity via the oral, dermal, and inhalation routes (Categories III or IV). It is neither a dermal irritant (Category IV), an eye irritant (Category IV), nor a dermal sensitizer.

Developmental toxicity was observed in rats and rabbits as growth retardations including delays in skeletal ossification; effects that have been observed with other HPPD inhibitors (e.g., pyrasulfotole). Neither the rat developmental study nor the rat 2-generation reproductive toxicity studies revealed any evidence of increased susceptibility. However, both adults and offspring in the 2-generation reproductive toxicity study exhibited ocular and liver toxicities seen in long-term studies.

In acute and subchronic neurotoxicity studies in adult rats, mild changes in the functional-observation battery parameters (grip strength and/or landing foot splay) were observed. However, such effects were not observed in either pregnant animals or offspring in a developmental neurotoxicity (DNT) study in rats. In both maternal animals and offspring, body-weight changes and/or food consumption were the primary effects noted and at the same dose tested. Decreased brain weights were observed in offspring on post-natal day 11 at the high dose only, but not at a later point in time, which is an indicator of a developmental delay and/or a secondary effect of the decreased body weight also observed in the offspring. There were no effects on pup swimming ability, learning, memory, motor activity, or auditory startle response at any dose, nor was there any evidence of neuropathology at any dose in the DNT study.

Isoxaflutole was negative in a variety of genotoxicity screening assays. In carcinogenicity studies, isoxaflutole induced liver and thyroid tumors in rats and liver tumors in mice; therefore,

isoxaflutole was classified as "likely to be a human carcinogen." However, based on the dietary exposure assessment, the agency has determined that when taking into consideration the amount of isoxaflutole one would be exposed to daily in their respective environment, the likelihood of developing carcinogenic effects are well below the agency's level of concern (LOC).

EPA has determined that reliable data show the safety of infants and children would be adequately protected if the Food Quality Protection Act Safety Factor (FQPA SF) were reduced to 1x for all exposure scenarios, except acute dietary for females 13–49 years of age for which an FQPA SF is retained but reduced to 3X. That decision is based on the following findings:

i. The toxicity database for isoxaflutole is complete.

ii. There are not residual concerns regarding neurotoxicity, including developmental neurotoxicity, based on the results of acute, subchronic, and developmental neurotoxicity studies.

iii. There is no evidence that isoxaflutole results in increased susceptibility following *in utero* exposure in a rat developmental study or in young rats in the 2-generation reproduction study. However, there was evidence of increased susceptibility following *in utero* exposure in a rabbit developmental study and a NOAEL for developmental effects was not identified in that study. To address the concern for increased *in utero* susceptibility and the lack of a NOAEL in the rabbit study, this study was selected for the acute dietary endpoint for females of 13–49 years of age and a 3X FQPA SF was retained for that population subgroup.

iv. There are no residual uncertainties identified in the exposure databases.

Dietary Exposure

In conducting the acute and chronic dietary exposure assessments, EPA used the food consumption data from the USDA 1994-1996 and 1998 CSFII. As to residue levels in food, EPA assumed that 100% of the crop was treated and that for all commodities residues were at tolerance levels. Even while using these highly conservative assumptions, EPA has concluded that chronic exposure to isoxaflutole from food and water will utilize 1% of the chronic population adjusted dose (cPAD) for all infants (<1 year old), the population group receiving the greatest exposure. The acute dietary exposure from food and water to isoxaflutole will occupy 2.4% of the acute population adjusted dose (aPAD) for females 13 to 49 years old, the population group receiving the greatest exposure. Therefore, the acute and chronic dietary exposures and risk estimates do not exceed the agency's LOC (i.e., $\geq$100% of the PAD). The resulting cancer risk estimate is 8×10^{-7} for the general U.S. population, which does not exceed the agency's target LOC (i.e., risk is below 10^{-6}).

Residential Exposure

There are currently no registered residential uses for isoxaflutole, and the newly registered soybean use is not likely to result in residential exposures.

Occupational Exposure

Occupational handler and post-application exposures are expected from the registered use on soybeans. Handler exposures were estimated assuming baseline clothing protection and the use of gloves, as required by the labeling (the label requires the use of gloves as personal protective equipment). Estimated risks for short- and intermediate-term risks are all below EPA's LOC for occupational handlers. Exposures for all post-application activities are also below EPA's LOC. Estimated cancer risks are below EPA's LOC for both occupational handlers and occupational post-application activities as well. A Restricted Entry Interval (REI) of 12 hours is required by the labeling in compliance with the Worker Protection Standard (WPS).

Aggregate Risk Assessment

Assessment of aggregate risk takes into account the combined risk potential that results from dietary exposure through food and water, as well as any additive residential exposures. Since there are no established residential uses for isoxaflutole or new residential uses being registered at this time, the acute, chronic, and cancer aggregate risks reflect only exposure to potential residues in food and drinking water. Therefore, the aggregate acute, chronic, and cancer risks are equal to the acute, chronic, and cancer dietary risks, which are well below EPA's LOC.

B. Assessment of Environmental and Ecological Risk

The environmental risk assessment evaluates the uses of isoxaflutole based on the submitted toxicology and environmental fate data, uses, application rates and methods, and current exposure models and assesses how the registered soybean use may affect aquatic and terrestrial animals and plants.

A detailed discussion and assessment of all the environmental and ecological criteria that went under review for the registered new use is provided in the agency documents titled:

- *Ecological Risk Assessment for the Isoxaflutole Proposed Section 3 Registration for Use on Soybeans and on Corn in Five Additional Southern States (South Carolina, Georgia, Alabama, Mississippi, and Louisiana*
- *Addendum to Ecological Risk Assessment for the Isoxaflutole Proposed Section 3 Registration for Use on Soybeans*
- *Revised Addendum to Ecological Risk Assessment for the Isoxaflutole Proposed Section 3 Registration for Use on Soybeans*

- *Addendum to Ecological Risk Assessment for the Isoxaflutole Proposed Section 3 Registration for Use on Isoxaflutole-Resistant Soybeans to Consider Data Generated with Ultra Coarse Nozzles*
- *Addendum to the 2016 Ecological Risk Assessment for the Isoxaflutole Proposed Section 3 Registration for Use on Isoxaflutole-Resistant Soybeans to Consider Proposed Label Restrictions and to Make an Effects Determination for Listed Species.*

These documents can be found under docket number EPA-HQ-OPP-2019-0398 at www.regulations.gov and a more detailed description of how these potential risks are assessed can be found at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/ecological-risk-assessment-pesticides-technical.

Environmental Fate Profile

The parent isoxaflutole rapidly degrades by abiotic hydrolysis and microbially mediated metabolism. It is moderately mobile, moderately soluble, and has low potential to volatilize from dry surfaces and water. The half-life of the isoxaflutole parent ranges from 0.32 to 4.2 days suggesting that it is non-persistent. Similarly, aerobic and anaerobic aquatic metabolism data show a rapid degradation of the parent. The parent isoxaflutole is stable to soil photolysis.

Isoxaflutole degrades into three degradates, two of which, RPA 202248 and RPA 205834, are structurally similar and appear to have herbicidal activity (RPA 205834 has only shown herbicidal activity in aquatic metabolism studies). As such, the residues of concern for terrestrial plants are the isoxaflutole parent as well as these two degradates. RPA 202248 is highly soluble and moderately mobile. It is also stable to hydrolysis and photolysis in aqueous systems, and hence poses a possible environmental concern. Because RPA 202248 is also more persistent than the parent compound in soil, estimates of isoxaflutole's mobility and solubility in soil are based on this degradate.

Ecological Risk Profile

The results from the ecological risk assessments indicate that the registered new use did not exceed EPA's LOC for risk to aquatic organisms (fish, invertebrates, aquatic-phase amphibians, or aquatic plants), and did not exceed EPA's LOC for risk to most terrestrial organisms (mammals, birds, reptiles, terrestrial-phase amphibians, terrestrial invertebrates and pollinators). As expected for an herbicide, isoxaflutole is toxic to terrestrial plants. Potential risks of concern have been identified for terrestrial non-target plants, including listed species (i.e., endangered, threatened, or candidate species) through run off and spray drift exposure routes to isoxaflutole. To address these concerns, the label includes language that is designed to minimize exposures to these non-target sensitive plants. For example, extensive state and county level restrictions that prohibit use in counties that contain any listed terrestrial plant or designated critical habitats eliminate any potential risk to listed plant species. Due to the unpredictability in movement of isoxaflutole, the possibility at or near the approved county borders for runoff to make its way into neighboring counties is a scenario the agency cannot be overlooked. Therefore, the new use

is not only prohibited from use in counties that contain listed terrestrial plant species or a designated critical habitat, but also in counties adjacent to those that contain listed plant species or a designated critical habitat. For those counties where over-the-top use of isoxaflutole on soybeans is registered, label restrictions and label language that informs and provides guidance for careful applications has been added to minimize unintended exposures from drift or runoff to non-target plants in neighboring areas. These label mitigations are discussed further in the Final Regulatory Decision and Label Requirements sections later in this document.

IV. Endangered Species Assessment

After integrating the county-level restrictions mentioned above, the agency determined that the registered new use of isoxaflutole on isoxaflutole-resistant soybeans will have *no effect* on 158 listed species located within 332 counties in 25 states where the approved new use has been be registered. It has also been determined that the registered new use will result in *no modification* to any designated critical habitats. Therefore, consultation with the U.S. Fish and Wildlife Service or the National Marine Fisheries Service (the Services) under Section 7 of the Endangered Species Act was not necessary for this action.

EPA has a specific process based on sound science that it follows when assessing risks to listed species for pesticides like isoxaflutole that will be used on fields where crops that are resistant to certain herbicides have been planted. The agency begins with a screening-level assessment that includes a basic ecological risk assessment consistent with its 2004 Overview of the Ecological Risk Assessment Process document [USEPA, 2004, available at http://www.epa.gov/endangered-species/ecological-risk-assesment-process-under-endangered-species-act]. That assessment uses broad default assumptions to establish estimated environmental concentrations of particular pesticides. If the screening-level assessment results in a determination that no levels of concern are exceeded, EPA concludes its analysis. On the other hand, where the screening-level assessment does not rule out potential effects (exceedances of the level of concern) based on the broad default assumptions, EPA then uses increasingly specific methods and exposure models to refine its estimated environmental exposures. At each step, EPA compares the more refined exposures to the toxicity of the pesticide active ingredient to determine whether the pesticide exceeds levels of concern established for listed aquatic and terrestrial species. If at any step in the screening-level assessment, a pesticide still exceeds the agency's levels of concern for listed species, EPA then conducts a species-specific refined assessment to make effects determinations for individual listed species. The refined assessment, unlike the screening-level assessment, takes account of species' habitats and behaviors to determine whether any listed species may be affected by use of the pesticide.

Effects Determinations

As discussed in the proceeding sections, an ecological risk assessment under the endangered species act was conducted on the registered new use. In that assessment, potential risks of concern were identified for listed terrestrial plants and designated critical habitats. This determination was based on the agency's refined risk assessment of isoxaflutole effects on non-

target plants exposed by spray drift and runoff conducted in 2016 and is accessible in the public docket at *www.regulations.gov* under docket number EPA-HQ-OPP-2019-0398. However, in an addendum to the 2016 risk assessment mentioned above, the agency reassessed the same data, but this time considered extensive label mitigation proposed by Bayer and supported by BASF. This mitigation limits the use of isoxaflutole on isoxaflutole-resistant soybeans to counties that do not contain a listed terrestrial plant or designated critical habitat as well as any county that adjoins a county that includes a listed terrestrial plant species or designated critical habitat. This mitigation alleviates the potential for exposure from spray drift and runoff to all listed terrestrial plant species as well as their designated critical habitats in the approved area of registration.

V. Resistance Management

The emergence of herbicide-resistant weeds is an increasing problem that has become a significant issue to growers. Management of these herbicide-resistant weeds, both by employing best management strategies to control established herbicide-resistant weeds and by slowing the development of new herbicide-resistant weeds, has been and continues to be a complex problem within agriculture. The concern that a scenario where the use of isoxaflutole on genetically modified crops may result in over-reliance on isoxaflutole and result in a large number of resistant weeds cannot be ignored. Currently in the United States there are already two weed species resistant to HPPD herbicides, Palmer amaranth (*Amaranthus palmeri*) and tall waterhemp (*Amaranthus tuberculatus*). Currently, there are very limited confirmed reports of HPPD-resistant weed populations. In an effort to address these issues, the final approved label has expanded language related to managing herbicide resistance.

The mechanism-of-action (MOA) using the WSSA Groupings is also placed on the label as described in PRN 2017-01. This provides critical information to growers and crop advisors when developing herbicide programs and following best management practices for weed resistance. It encourages the user to rotate between effective MOAs to reduce the buildup of resistance weeds. All currently required application parameters and product information are clearly expressed on the label, including minimal effective dose, dose per crop cycle or per year, and number of applications per crop cycle or per year. This information is critical to allow the user to know how many applications and what amounts can be applied in order to develop an effective Integrated Pest Management (IPM) plan for the season and entire year. Additionally, label statements describing Best Management Practices (BMP) from WSSA and the Herbicide Resistance Action Committee (HRAC) are included. This provides the users with readily available information about managing resistance as part of Bayer's and ultimately BASF's education and stewardship program. Other label language refers users to other sources for information about resistance. Once BASF take control of the soybean registration, they will be required as part of their Herbicide Resistance Management plan to report new cases of resistance to the agency, as well as provide educational and training materials developed for growers and users to the agency.

VI. Greater-than-Additive Effects

While there are pesticide formulation synergists designed to enhance pesticidal activity, true synergism is considered rare. Therefore, even though pesticides are often tank mixed, EPA continues to evaluate the ecological effects of each pesticidal active ingredient independently, and follows the National Research Council's recommendation that "In the absence of any data that would support the hypothesis of a synergistic interaction between the pesticide active ingredient and other mixture components, the effects analysis should proceed on the assumption that the components have additive effects."

However, there have been cases where pesticide producers have been granted patents by the U.S. Patent and Trademark Office based on claims that specific mixtures of pesticides elicited enhanced pesticidal or synergistic activity towards target pest(s). As a result, EPA is evaluating these synergistic claims on a case-by-case basis to determine if the available scientific data used to support such claims is appropriate and adequate to assess risks to non-target organisms under EPA's guidelines. If there is evidence to suggest that there are potential synergistic effects from certain combinations, then EPA may require review of these data since the available data on its individual components may not provide adequate information on the effects to non-target organisms.

The newly registered use of isoxaflutole on isoxaflutole-resistant soybeans allows for tank mixing with other pesticides. As such, Bayer completed a search of U.S. patent data to identify any claims of synergy (or more than additive effects) with other currently registered pesticides according to EPA criteria and submitted corresponding data to EPA. Upon review of the submitted data, the EPA concluded that at this time, all patent data claiming synergy with isoxaflutole does not affect the final determinations made in the agency's ecological risk assessment.

VII. Benefits

Post-emergent weed control is an important component for successful production of row crops, such as soybeans. This registered use of isoxaflutole is a new tool that may be helpful for controlling emerged weeds. Soybeans and more specifically genetically engineered herbicide resistant soybeans are an extremely important agricultural commodity in the United States and around the world. According to the USDA National Agricultural Statistics Service, soybeans are grown on approximately 76.5 million acres, and USDA estimates the gross value of 2018 soybean production at approximately 39 billion dollars. USDA's Economic Research Service describes soybeans as the world's largest source of animal protein feed and the second largest source of vegetable oil. The United States is the world's leading soybean producer and exporter, and soybeans are grown throughout the United States with more than 80% of soybean acreage concentrated in the upper Midwest.

Growers throughout these areas of the United States are currently experiencing yield and economic losses due to weeds developing resistance to heavily used herbicides such as

glyphosate. The need for additional tools to manage these resistant weeds has become even more important as herbicide resistance has become a significant financial, production, and pest management issue for the nation's soybean growers. WSSA and other weed control experts warn that the problem of weed resistance (most notably with glyphosate) is increasing, and significant economic consequences will continue to rise without effective alternatives for weed control.

Currently, there are no HPPD herbicides labeled for over-the-top use on soybeans. Therefore, for those growers that do not already have HPPD-resistant weeds, the use of isoxaflutole will provide a new tool for weed control in soybeans. This new use can be used in rotation with different modes of action for resistant management purposes directed towards non-HPPD resistant biotypes. In addition to being an effective tool to control some of the most difficult to control weeds in soybeans, such as horseweed and common lambs quarters, the registered new use could also be an effective tool to control weeds already resistant to other herbicides, including glyphosate, which could ultimately aid in crop production and reduce economic losses to soybean growers throughout the country.

From a benefits standpoint, EPA analysts have concluded that isoxaflutole can be a useful tool for soybean farmers to fight herbicide resistant weeds where HPPD-resistance is not a concern. Isoxaflutole also provides broad spectrum control of several grass and broadleaf weeds, a flexible use pattern (pre- or post-crop emergence), and residual activity, making it an effective foundation component in an Integrated Weed Management program.

VIII. Response to Comments

The Agency received 54 comments in response to the public participation process (Docket ID EPA-HQ-OPP-2019-0398) regarding the EPA's proposed decision for the application to register the use of isoxaflutole on isoxaflutole-resistant soybeans. Comments received, while varying in specific details, were generally in favor of the decision to register the new use which will provide growers with an additional tool to control both broadleaf and grass weeds. The EPA welcomes input from the public during the decision process when registering significant new uses for registered pesticides and is committed to thoroughly evaluating these comments and determining whether mitigation measures are necessary to meet the applicable statutory standards. The EPA reviewed and evaluated the comments received during the comment period before issuing this final regulatory decision. Since many of the comments covered similar issues, the comments were grouped into major topic areas. For the agency's response to these comments, please see *Response to Comments Received on the New Use of Isoxaflutole on Isoxaflutole-Resistant Soybeans* dated March 25, 2020 which is accessible in the public docket at *www.regulations.gov* under docket number EPA-HQ-OPP-2019-0398.

IX. Registration Decision

In accordance with FIFRA, a pesticide registration is granted only when the agency can make a determination that the new pesticide use will not cause unreasonable adverse effects to human health or to the environment, taking into account the economic, social, and environmental cost

and benefits of the new use. Under FIFRA, the agency is charged with balancing the uncertainties and risks posed by a pesticide's use against its benefits and determine if the benefits outweigh the risks before granting a registration. In the case for the new uses of isoxaflutole on isoxaflutole-resistant soybeans, and in consideration of all best available data and assessment methods, the EPA determines that its decision to register these uses meets the requirements of FIFRA.

The database submitted to support the assessment of human health risk is sufficient for a full hazard evaluation and is considered complete and adequate to evaluate risks to infants and children. The agency has not identified any risks of concern in regard to human health, including all population subgroups, or for occupational handlers.

In terms of ecological risk, no risks of concern were identified for birds, reptiles, amphibians, invertebrates, or mammals from the new use. Risks of concern were identified, if exposure occurs through drift or runoff to non-target plants, but plant risk is typical of herbicides in general. Additionally, the protections afforded by the labeling should minimize these exposures. For example, risks to listed terrestrial plants are mitigated because the approved label does not allow the newly registered use in counties that contain a listed terrestrial plant species, a designated critical habitat, or counties adjacent to counties that contain a listed terrestrial plant species or a designated critical habitat. In most cases, this effectively puts a buffer of several miles between the approved use sites and all listed terrestrial plant or designated critical habitats. In counties where isoxaflutole can be used, label restrictions and label guidance are added that are intended to protect non-target plants by minimizing unintended isoxaflutole movement off the treated site. Because isoxaflutole is phytotoxic at low levels, and because there is potential for isoxaflutole to contaminate irrigation water and ground water through leaching and surface water runoff, labeling advisories and restrictions are in place to protect neighboring and irrigated crops, especially highly sensitive vegetable crops. For example, the label restricts against use in areas that are prone to vulnerable conditions, such as coarse soils or high ground water tables that might promote the movement of the chemical off the treatment site. Surface and ground water advisories exist in order to further inform users of the inherent risks of isoxaflutole's mobility and solubility. Drift management strategies, including a prohibition against aerial applications or through irrigation systems, are intended to further reduce unintended movement off-site. Observed together, these requirements should profoundly reduce off-site exposures and contain isoxaflutole on the treatment site.

As referenced above in the Resistance Management section of this document, the EPA also recognizes that the new use could potentially increase the populations of isoxaflutole-resistance weeds and develop isoxaflutole-resistance in other target weeds. Because isoxaflutole is already registered on corn, EPA is concerned with weed resistance developing as a result of use on both corn and soybeans. The reason for this concern is that corn and soybeans are commonly rotated in the same fields, which helps control weed resistance because different herbicides (with different modes of action) are used to control weeds in grass crops versus in broadleaf crops. When the same herbicide is routinely used on both crops in the same fields, weed resistance management is likely to develop much more quickly because the same mode of action is

consistently being applied. In addition, experience with glyphosate demonstrates that consistent herbicide use on genetically-engineered crops can be very widespread and involve extremely high acreage, which can further promote the development of herbicide resistance in weeds. Therefore, resistance management label language (including best practices, MOA information, and instructions on field-scouting, identification of surviving weeds, and reporting product performance issues) has also been approved to preserve and maximize the benefits of this new tool while protecting against the potential risk of weeds developing resistance to isoxaflutole. Also, an isoxaflutole-specific resistance-management stewardship plan shall be implemented by the registrant which include components on education/training, monitoring, and remediation of product non-performance incidents. Annual reports are also required in order for the agency to monitor the effectiveness of the stewardship program and the potential development of weed resistance. Communications to users and other stakeholders on weed-resistance incidents are also required in order to quickly address resistance issues. Lastly, a 5-year registration has been approved so that the agency can address any unexpected weed resistance issues that may result from the new use before granting a registration extension; or alternatively, allow the registration to terminate if necessary.

On the benefits side of the analysis, soybean is an extremely important agricultural commodity in the United States and the world, and the new use of isoxaflutole on isoxaflutole-resistant soybeans is expected to become an important part of a resistance management strategy for this crop. Being grown in millions of acres in the United States with an estimated gross value in the billions, soybeans serve as a leading animal feed and one of the leading sources of vegetable oil. The United States produces more soybeans than any other country and is the second-leading exporter. However, resistance to glyphosate, the current market leader in soybeans, is having severe economic consequences in soybean production. The WSSA and other weed control experts warn that the problem of glyphosate resistance is increasing, and that significant economic consequences will continue to increase without effective alternatives for weed control. The use of isoxaflutole would provide a new tool for weed control in soybeans which could be used in rotation with different modes of action for resistant management purposes directed towards non-HPPD resistant biotypes. In addition to being an effective tool to control some of the most difficult to control weeds in soybeans, including some noxious weeds that are also resistant to other herbicides, this registered new use could also be an effective tool to control weeds already resistant to glyphosate. This could ultimately aid in crop production and reduce economic losses to soybean growers throughout the country. EPA finds these benefits important.

After weighing all the risks of concern against the benefits of the new use, the EPA finds that, when the mitigation measures for these uses are applied, the benefits of the use of the pesticide outweighs any remaining minimal risks. The agency has not identified any risks of concern for human health, including all population subgroups, or for occupational handlers. Isoxaflutole is not likely to result in risk to non-target animals including fish, invertebrates, amphibians, mammals, birds, reptiles, and pollinators. Risks to non-target plants are not unreasonable when considered in conjunction with the protections afforded by the label mitigation and the benefits of a new tool for weed control and resistance managment in soybeans. Therefore, the registration of this new use will not generally cause unreasonable adverse effects on human health or the

environment. The EPA believes that the available data and scientific assessments as well as the overall considerations for benefits for weed management in this important crop support a FIFRA Section 3(c)(5) registration finding for the new use.

Therefore, EPA is granting a 5-year registration under FIFRA 3(c)(5) for the new use of isoxaflutole on isoxaflutole-resistant soybeans, with conditions requiring an herbicide resistance management plan with annual reporting and geographic limitation for use only in specified counties in the following 25 states: AR, CO, GA, IN, KS, KY, LA, MI, MN, MO, MS, MT, NC, ND, NE, NM, OH, OK, PA, SD, TN, TX, VA, WI, WV.

X. Registration Terms and Conditions

The agency has required that the registration notice contain terms of registration, state restrictions, resistance management stewardship plan, and annual reporting requirements. Details are provided below.

Data requirements

No additional guideline data are required to support this final decision. However, while there are no outstanding data requirements at this time, isoxaflutole is currently being evaluated under the agency's registration review process. During any point of this process, the agency may deem it necessary to request further data in order to support its registration review decision. Any additional data requested through this process would be handled in accordance with the registration review process.

Geographic limitation

The agency determined that isoxaflutole may only be registered for use on isoxaflutole-resistant soybeans grown in a limited number of states and specific counties within those states for which an endangered species assessment has been conducted and a "*no effect*" determination has been made. For a list of the approved states and counties, please refer to the final approved label posted to docket ID number EPA-HQ-OPP-2019-0398 at www.regulations.gov.

Stewardship and Annual Reporting

To mitigate the potential risk of developing isoxaflutole-resistant weeds as a result of the new use, Bayer and subsequently BASF must implement an herbicide resistance management plan, including education and training, along with investigation and remediation of suspected resistant weeds.

Annual reports are required to be submitted to the EPA in order for the agency to monitor the effectiveness of the stewardship program and the potential development of weed resistance. Communications to users and other stakeholders on weed-resistance incidents are also required in order to quickly address resistance issues.

The reports must include the number of cases of suspected and/or confirmed weed resistance by weed species, county, and state. Case summaries on the investigation and remediation of these incidences must also be provided. These reports will provide stakeholders with access to information on suspected and confirmed resistance in a timely manner so that they can proactively address the problem.

X. Label Requirements

As discussed in the sections above, EPA is requiring additional label restrictions and label language to provide safety and guidance in order to prevent exposures to listed plants. Therefore, the following label mitigation has been added to the end-use product label for the isoxaflutole-resistant soybean use.

> This product must only be used on isoxaflutole-resistant soybeans ***in specifically designated counties*** in the following states: AR, CO, GA, IN, KS, KY, LA, MI, MN, MO, MS, MT, NC, ND, NE, NM, OH, OK, PA, SD, TN, TX, VA, WI, WV.

Isoxaflutole has been classified as a Restricted Use Pesticide. Therefore, the product must be applied by certified applicators or workers under their direct supervision.

Because the mobility and solubility of isoxaflutole can promote its tendency to leach and run off treated areas, the following surface and ground water advisories are intended to increase user awareness of vulnerable conditions that should be avoided to help protect water resources:

> "This chemical is known to leach through soil into ground water under certain conditions as a result of agricultural use. Thus, use of this chemical in areas where soils are permeable, particularly where the water table is shallow, may result in ground water contamination."

> "Isoxaflutole residues can contaminate surface water through spray drift. Under some conditions, isoxaflutole residues may also have a high potential for runoff into surface water (primarily via dissolution in runoff water), for several weeks after application. These include poorly draining or wet soils with readily visible slopes toward adjacent surface waters, frequently flooded areas, areas over-laying extremely shallow ground water, areas with infield canals or ditches that drain to surface water, areas not separated from adjacent surface waters with vegetated filter strips and areas over-laying tile drainage systems that drain to surface water."

In order to prevent drift of isoxaflutole to neighboring areas, aerial application is prohibited. Only ground applications are permissible.

The following types of label restrictions are in place to prohibit application scenarios that could promote exposure to neighboring plants, including crops, through runoff or contaminated irrigation water:

Numerous restrictions involve prohibitions against use around vulnerable soil types when they are located in areas with shallow water tables. Water table depths in combination with specific soil types are described to give the applicator detailed instructions to identify areas where applications are allowed versus areas where applications are prohibited.

The product is restricted from use through any type of irrigation system.

Applicators are restricted from using flood or furrow irrigation to apply, activate or incorporate this product.

Applicators are restricted from irrigating this product into coarse soils at planting time when soils are saturated.

To protect agricultural workers from accidental exposures when working in the treated field, the label requires the use of protective gloves as personal-protective equipment (PPE). Also, the REI is 12 hours.